Effects of marijuana extract and tetrahydrocannabinol on electroencephalographic sleep patterns

Marijuana extract, given in daily doses containing 70 to 210 mg delta-9-tetrahydrocannabinol (THC), induced effects on sleep that were virtually identical to those produced by the same doses of relatively pure (96%) THC. Both drugs reduced eye movement density with some tolerance developing to this effect. Stage 4 tended to increase with drug administration. Abrupt withdrawal led to extremely high densities of eye movement, increased rapid eye movement (REM) durations, and a sharp but transient fall in stage 4 to baseline levels. These effects may be useful in the elucidation of the pharmacology of sleep. The effects on sleep of THC administration (but not withdrawal) closely resemble those induced by lithium. For this reason, we suggest further studies of THC in affective disorders. Evidence available thus far suggests that THC produces dysphoric symptoms in unipolar but not in bipolar depressed patients; these differences in response may prove of diagnostic value. An adequate therapeutic trial of THC in bipolar depressed patients has not yet been carried out.

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We recently described the effects of relatively pure delta-9-tetrahydrocannabinol (THC) in doses up to 210 mg/day on the sleep patterns of male subjects with a history of drug use.[9] Some investigators[16] have asserted that the pharmacologic effects of the THC mixed with the other natural constituents of the plant differ from those of THC alone. However, most of the evidence suggests that this is not the case and that most, if not all, of the physiological and behavioral effects of marijuana can be attributed to THC.[13] Since we found that THC in high dosage induced marked alterations of electroencephalographic (EEG) sleep patterns, we wished to determine whether marijuana extract containing the same amount of THC and administered under the same conditions would induce the same or different effects.

The results of these studies will be presented in considerable quantitative detail. Our reasons for doing so is that marked and, possibly, unique effects were induced by high-dose THC on human sleep patterns. Present knowledge of

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Table I. *Subjects studied in month long protocol*

Condition	*No. subjects*	*No. nights recorded*
Baseline	2 extract, 4 THC	5 (nts. 1-5)
Initial dose (70 mg/day)	2 extract, 4 THC	3 (nts. 6-8)
Initial high dose (210 mg/day)	2 extract	3 (nts. 9-11)
Long-term high dose (210 mg/day)	4 extract, 7 THC	3 (nts. 19-21)
Withdrawal	4 extract, 7 THC	3 (nts. 22-24)
Late withdrawal	2 extract	3 (nts. 30-32)

sleep pharmacology is insufficient to explain these results in terms of neurotransmitter or other brain mechanisms. We cannot predict which of our data will be most useful for future understanding. For this reason, and because the experiments would be difficult and extraordinarily expensive to repeat, we have thoroughly documented our findings.

Methods

Subjects. The subjects who received marijuana extract ("extract Ss") were 4 experienced male marijuana users. They were paid volunteers, screened to eliminate those with medical or psychiatric illness, who agreed to be hospitalized on a psychiatric ward for 21 to 32 days. Their ages ranged from 21.7 to 31.2 yr with a mean of 25.6 yr. The sleep data of the extract Ss were compared with those obtained from 7 similar Ss ("THC Ss") who had received pure THC.[9]

Drug

A crude ethanolic marijuana extract was obtained from the National Institute of Drug Abuse. It contained 29% THC, 1.5% cannabinol, and 2.8% cannabidiol as assayed by gas-liquid chromatography. Doses of 10 mg and 30 mg THC content were given in gelatin capsules with the marijuana extract dissolved in 0.4 ml of ethanol. Placebo capsules contained only the 0.4 ml ethanol. The effects produced by the extract were compared to those previously obtained with THC. It is important to note that the THC used in our earlier work was only relatively pure, consisting of 96% THC and fractional percentages of other cannabinoids, including delta-8-THC, cannabichromine, etc. While these other substances are not known to induce major psychotropic effects, their presence in both the THC and the extract preparations permits the possibility that it is they, rather than the THC, that are responsible for the effects on sleep, although this possibility would seem quite remote.

Drug schedule

Subjects were studied at the points in the month long protocol shown in Table I. The initial dose of the drugs was administered as follows: 8 A.M. (10 mg); noon (20 mg); 4, 8, 11:30 P.M. and 4 A.M. (10 mg each). For 210 mg/day, the dose at each time was tripled. On the first withdrawal night, the 210-mg schedule was followed until the 8 P.M. dose when placebo substitution was initiated. Placebo was continued throughout the withdrawal period on the same schedule. This protocol allowed data from extract Ss to be compared with data from the THC Ss under 4 of the 6 conditions, viz, baseline, initial dose, long-term high dose, and withdrawal.

Sleep recording and scoring

Sleep recording and scoring were carried out according to methods previously described.[10] One or two EEG and two eye movement channels were recorded for each S. Data were obtained with Beckman type R dynographs run throughout the night at a paper speed of 15 mm/sec, a gain of 8 mm/50 uV and time constant of 0.3 sec. The ink-written records were coded and scored without knowledge of drug condition. FM tape recordings were also obtained for future computer analysis of EEG and eye movement.

Results

The pattern of effects of marijuana extract on sleep was virtually identical to of THC. The

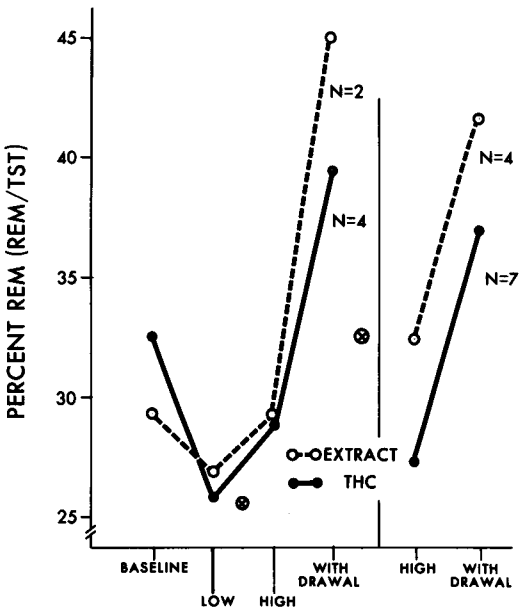

Fig. 1. Comparison of the effects on percent of time in REM sleep induced by pure THC and by marijuana extract containing the same dose levels of THC. The experimental conditions are described in the text. Since baseline levels differed for THC and extract Ss, attention should be directed to the pattern of change across drug conditions. Both THC and marijuana extract induced an initial decrease in percentage REM time to which partial tolerance developed. Withdrawal was associated with an increase above baseline levels (rebounds). Circled Xs represent data available for two Ss under initial high dosage of 210 mg and late withdrawal (withdrawal nights 8 to 10). The data show that, after 3 nights on the 70-mg dose, there was little further suppression when the dose is increased to 210 mg; the later withdrawal data showed a return (to a somewhat high baseline level) after 1 wk. The baseline and high dosage levels for THC and marijuana extract were not significantly different and the changes across experimental conditions were identical for both drugs.

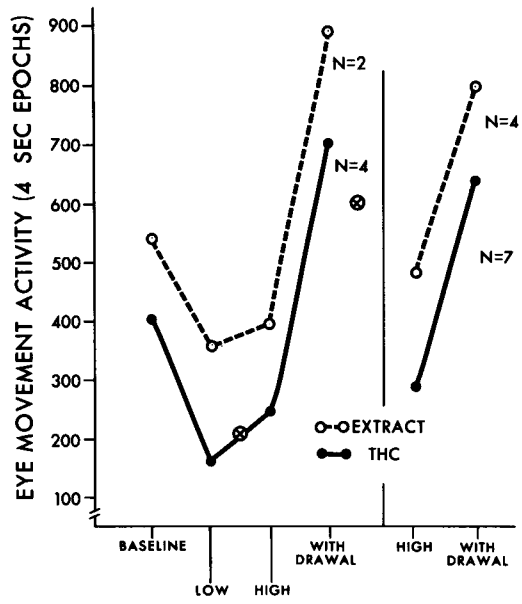

Fig. 2. Effects of THC and marijuana on eye movement activity for the same experimental conditions described in Fig. 1. Differences in baseline and long-term high dose for the two drugs were not significant and the trend across experimental conditions was identical for both. The initial high-dose data also indicated substantial tolerance after 3 days on 70 mg and the late withdrawal data suggest return to baseline after 1 wk. The percentage change from baseline for EM activity is considerably greater than that for REM time.

effects of both THC and extract were most pronouced for stage 4 sleep, eye movement activity during REM sleep *(EM activity)*, and duration of REM sleep *(REM time)*. Figs. 1 to 3 compare the effects for THC and extract for these variables across drug conditions. The baseline levels of the Ss differ (but not significantly), as often occurs in sleep data drawn from small samples. Attention should therefore be directed to the patterns of change in response to administration and withdrawal of both THC and extract. With the exception of a single point (long-term high dose) on the stage 4 graph (Fig. 3), the changes produced by THC and extract were identical. Since THC and extract produced the same effects, the results were subjected to combined as well as separate statistical analyses in Tables I to IV. These tables also give the values for the initial high dose and late withdrawal conditions, available for 2 of the extract Ss.

1. Total sleep time and time awake. Table II shows that time from lights out to onset of sleep *(sleep latency)* was not significantly altered by drug except during immediate withdrawal, when it almost doubled. This increase in *sleep*

latency, with *time in bed* and *time awake after sleep onset* constant, produced a significant reduction in *total sleep time.* The increase in *sleep latency* was also responsible for the increase in the measure *total time in bed spent awake.* It is of special interest that there was no increase in the amount or percentage of *time awake after sleep onset* in the withdrawal condition. This finding is noteworthy in view of the fact that all Ss were awakened for the 4 A.M. dose of placebo as they had been for the drugs. Such interruptions of sleep might have been expected to lead to prolonged awakenings had arousal levels been increased substantially.

2. *Measures of REM sleep.* Table III shows that initial intake of 70 mg THC, either in pure form or in extract, reduced *REM time* and, to a considerably greater extent, suppressed EM. Thus, for the combined data, *percent REM time* was reduced by 18% (from 31.4% to 26.1%), whereas total *EM activity* was reduced by 49% (from 450.4 to 228.6 U) and *EM density* by 40% (from 22.8 to 13.6). Increasing the dose to 210 mg after 3 days of 70 mg produced some increase in these effects. However, since these increments were relatively small in the face of a large increase in dosage, it seems probable that some tolerance had developed during the 3 days on 70 mg. All eye movement measures were lowered by THC, including *total EM (4-sec epochs), EM density* [which equals *total EM (4-sec epochs)* × 100, divided by number of 4-sec epochs of REM sleep], and the tendency of EM to occur in bursts [*total EM (4-sec epochs),* divided by number of 20-sec epochs with at least one EM].

With continued drug intake, *REM time* and *EM activity* moved toward but did not reach baseline levels. During long-term high dosage *REM time* was 13% below baseline. *EM activity* and *EM density* were more substantially suppressed, being 34% and 23% below baseline, respectively, during long-term high dosage. Abrupt withdrawal led to a substantial increase in *REM time* and to an even more marked increase in the EM measures above baseline ("rebound" phenomena).

The comparison of sleep patterns under high dosage and withdrawal for extract and THC Ss combined (N = 11) demonstrates the powerful

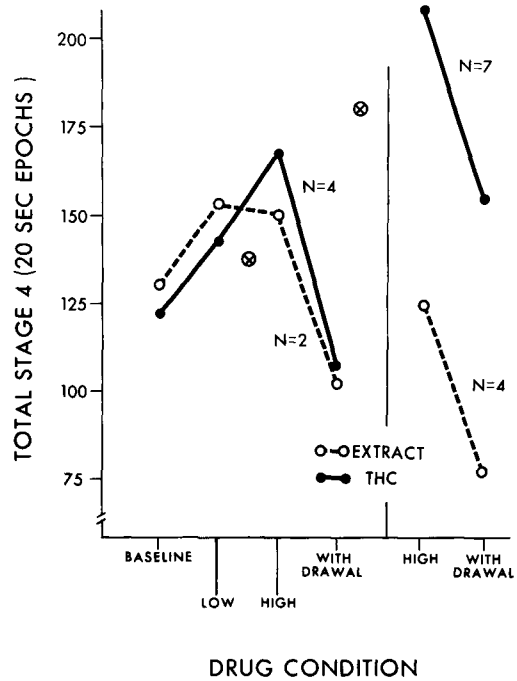

Fig. 3. Effects of THC and marijuana extract on stage 4 sleep. The experimental conditions are described in Fig. 1. THC and marijuana extract showed the same pattern of effects with the exception of the high-dosage condition; in view of the difficulty in scoring stage 4 EEG, no weight can be placed on this statistically insignificant difference. The high level of stage 4 during late withdrawal suggests that this variable may not return to baseline as rapidly as does REM time.

effects of THC under these conditions of dosage and around-the-clock administration. We cannot state with certainty how long the withdrawal effects last. None of the REM sleep variables during late (day 8 through day 10) withdrawal showed significant differences from baseline; however, these data were based on only 2 Ss.

In view of the widely held notion that high levels of REM sleep during withdrawal of hypnotics may themselves cause nightmares and disturbed sleep,[15, 21] it is worth emphasizing that not a single S complained of these symptoms in our laboratory during withdrawal from THC or extract. Thus, high REM levels are not sufficient causes of either nightmares or increased awakening in the sleep laboratory. However, some of these and similar Ss complained of nightmares and disturbed sleep during withdrawal from THC and extract when

Table II. *Measures of sleep and waking for THC and marijuana extract, separately and combined*

Time in min	*A. THC (N = 4) EXT (N = 2) COMB (N = 6)*					
	Baseline (b)	*Low dosage (l)*	*Initial high dosage (i)*	*Long-term high dosage (h)*	*Initial withdrawal (w)*	*Long-term withdrawal*
Total time in bed						
THC	450.4	445.3	—	446.3	450.6[l]	—
EXT	449.9	448.7	450.8	450.2	449.7	451.7
COMB	450.3	446.4	—	447.7	450.3[l]	—
Sleep latency						
THC	13.8	14.7	—	31.7	47.5[l,h]	—
EXT	15.2	8.4	8.6	12.4	55.0[i]	22.2
COMB	14.3	12.6	—	25.3	50.0[b,l,h]	—
Total sleep time						
THC	429.8	417.1	—	404.0	393.2	—
EXT	427.6	428.0	423.9	410.3[i]	379.9	420.9
COMB	429.0	420.8	—	406.1[b]	388.8[b,l,h]	—
Total time awake						
THC	20.7	28.2	—	42.4	57.4	—
EXT	22.2	20.7	26.9	39.8[i]	69.8	30.8
COMB	21.2	25.7	—	41.6	61.5[b,l,h,]	—
Time awake after sleep onset						
THC	6.9	13.5	—	10.7	9.8	—
EXT	7.0	12.2	18.3	27.5	14.8	8.7
COMB	6.9	13.1	—	16.3	11.5[b]	—
Total number of awakenings						
THC	1.2	1.2	—	1.2	1.3	—
EXT	1.5	1.8	2.2[l]	2.3	2.0	1.7
COMB	1.3	1.4	—	1.6	1.6	—
Av. duration of awakenings						
THC	5.0	8.2	—	7.4	6.8[b]	—
EXT	4.5	7.8	8.9	12.0[b]	6.5[b,h]	4.3
COMB	4.8	8.1	—	8.9	6.7[b]	—

P values are based on paired, 2-tailed t tests. Group means are based on means for 3 nights for each S for each condition.
b,*b* differs from baseline $p < 0.05$, $p < 0.01$, resp.
l,*l* differs from low dosage $p < 0.05$, $p < 0.01$, resp.
i,*i* differs from initial high dosage $p < 0.05$, $p < 0.01$, resp.
h,*h* differs from long-term high dosage $p < 0.05$, $p < 0.01$, resp.
w,*w* differs from initial withdrawal $p < 0.05$, $p < 0.01$, resp.

sleeping on the psychiatric ward, a much noisier environment.*

3. Measures of slow-wave (or NREM) sleep. Table IV shows that total slow-wave or NREM sleep increased as REM declined during drug administration, and decreased significantly during the REM sleep "rebound" in withdrawal. It is of interest that the distribution of NREM sleep among stages 2, 3, and 4 showed remarkably little change; the percentages of NREM sleep made up by these stages on high drug dosage closely resembled those in baseline. This fact would have been obscured had the percentage of stages 2 to 4 been computed with total sleep (REM + NREM) as the denominator, rather than NREM alone. During withdrawal, total amounts of stages 2, 3, and 4 declined (the changes for 2 and 4 being

*Jones, R. T.: Observations to be published.

B. THC (N = 7) EXT (N = 4) COMB (N= 11)		
Long-term high dosage	*Initial withdrawal*	*Long-term high dosage vs initial withdrawal (p)*
447.2	449.6	NS
449.9	449.0	NS
448.2	449.4	NS
31.9	54.7	0.005
20.7	52.2	0.019
27.8	53.7	0.0001
406.4	384.83	0.043
406.3	365.9	NS
406.4	377.6	0.01
40.8	65.4	0.02
43.6	83.1	NS
41.8	71.8	0.003
8.9	10.7	NS
22.9	30.9	NS
14.0	18.1	NS
1.3	1.8	NS
3.1	2.6	NS
1.9	2.1	NS
6.4	6.2	NS
8.5	10.4	NS
7.2	7.7	NS

statistically significant), but the percentages of stages 2 and 4 remained unchanged. In contrast, a relatively smaller and insignificant decrease in total stage 3 led to a significant increase in per cent stage 3 on withdrawal. We emphasize the fact that the architecture of NREM sleep was essentially normal under both high-dosage THC and extract and after abrupt withdrawal, since this fact distinguishes THC effects from those of sedative-hypnotic agents.

4. Temporal patterns. There were no significant differences across drug condition in the number of sleep cycles completed. Table V gives the main cycle data for THC and extract studies combined for 6 Ss under baseline and for the 11 Ss under high dosage and withdrawal conditions. This analysis was facilitated by use of the SLPTAB computer program,[23] which tabulates visually scored sleep data for successive sleep cycles as well as the entire night. Under high dose, the first NREM period ($NREMP_1$) was somewhat short compared to baseline as a result of early REM onset (<10 min) in 3 of the 7 Ss who received pure THC. (It may be of interest that none of the 4 extract Ss showed this effect.) The reduced $NREMP_1$ under high dose occurred even though overall *REM time* in these Ss decreased. This finding gives further support to our long-expressed view[5, 7, 11] that early REM onset does not necessarily reflect increased REM "pressure." (Since the REM latency depends upon the duration of $NREMP_1$, early REM onset may instead represent decreased NREM "pressure.") Under withdrawal, $NREMP_1$ became still shorter, and was significantly lower than both high-dosage and baseline values. Under high dosage, $NREMP_4$ was longer than in baseline, whereas it was virtually identical to the baseline value under withdrawal. *Total stage 4* was abnormally low in the first cycle during withdrawal; this was a necessary consequence of the extremely short $NREMP_1$. The trends for *total stage 4* across cycles 2 to 4 were unremarkable except for the relatively high values under THC.

Normally, the first rapid eye movement sleep period ($REMP_1$) is shorter than subsequent periods in young adults.[4] Table IV shows that this was the case under baseline and high dosage, but not under withdrawal, where $REMP_1$ was usually long. The $REMP_1$ under baseline and high dosage, while shorter than that under withdrawal, was still somewhat longer than the norm of 12 min (±2 min SE) expected for this age group.[6] This finding, along with the rather high baseline percentages for REM, raises the possibility that these Ss were undergoing some degree of withdrawal during baseline from drugs used at home.

Although each REMP under withdrawal was somewhat longer than that under high dosage, only for the first period was this difference statistically significant ($p < 0.05$). In contrast, *EM density* under withdrawal was significantly higher than that under high dosage for all 4

Table III. *Measures of REM sleep for THC and marijuana extract, separately and combined*

	A. THC (N = 4) EXT (N = 2) COMB (N = 6)					
	Baseline (b)	*Low dosage (l)*	*Initial high dosage (i)*	*Long-term high dosage (h)*	*Initial withdrawal (w)*	*Long-term withdrawa*
EM latency (min.)						
THC	79.9	80.2	—	59.0	33.4^{b,l,h}	—
EXT	60.6	68.4	103.8	63.1	15.6	52.9^{w}
COMB	73.5	76.3	—	60.4	27.5^{b,l,h}	—
REM time (min)						
THC	139.2	107.7^{b}	—	117.1^{b}	154.0^{l,h}	—
EXT	125.5	114.7	108.4	115.9	169.6	136.2
COMB	134.6	110.0^{b}	—	116.7^{b}	159.2^{b,l,h}	—
Percent REM time						
THC	32.4	25.8^{b}	—	28.9^{b}	39.5^{l,h}	—
EXT	29.4	26.9	25.5	28.4	45.1	32.5^{h}
COMB	31.4	26.1^{b}	—	28.7^{b}	41.4^{b,l,h}	—
Total EM (4-sec epochs)						
THC	405.2	162.2^{b}	—	247.1^{b,l}	704.2^{b,l,h}	—
EXT	541.0	361.4	214.3^{b,l}	396.2^{l,i}	893.0	601.2^{l,i}
COMB	450.4	228.6^{b}	—	296.8^{b,l}	767.1^{b,l,h}	—
EM density						
THC	19.6	9.5^{b}	—	14.3	30.7^{b,l,h}	—
EXT	29.1	21.8^{b}	16.9	23.7^{l}	35.3	29.8
COMB	22.8	13.6^{b}	—	17.4^{b,l}	32.2^{b,l,h}	—
Total EM (4-sec epochs)* Total EM (20-sec. epochs)						
THC	2.5	2.0^{b}	—	2.4	2.8^{b,l,h}	—
EXT	2.6	2.1	2.2	2.5	2.8	2.6^{l}
COMB	2.5	2.1^{b}	—	2.4^{l}	2.8^{b,l,h}	—

p values are based on paired, 2-tailed t tests. Group means are based on means for 3 nights for each S for each condition.
b,*b* differs from baseline $p < 0.05$, $p < 0.01$, resp.
l,*l* differs from low dosage $p < 0.05$, $p < 0.01$, resp.
i,*i* differs from initial high dosage $p < 0.05$, $p < 0.01$, resp.
h,*h* differs from long-term high dos. $p < 0.05$, $p < 0.01$, resp.
w,*w* differs from initial withdrawal $p < 0.05$, $p < 0.01$, resp.
*indicates tendency for EM to occur in bursts.

REMPs. This result is further testimony to the powerful effect of THC on eye movement during sleep.

5. EEG fast activity. In our previous report,[9] we noted that the EEG fast activity characteristic of sedative-hypnotics such as barbiturates and benzodiazepines was not apparent with THC. With marijuana extract, fast activity was observed in the sleep records of two Ss. In one S, fast activity was present under baseline and increased during drug administration. In the second case, it was apparent only during the drug period. However, the amount of fast activity in these 2 Ss was far less than is usually observed with sedative-hypnotics. Thus, it is possible that marijuana extract stimulates fast EEG activity; if so, the effect is extremely slight. Further information on this issue must await the spectral analysis to be carried out on the waking EEG with a larger number of Ss.

Discussion

Our findings indicate that relatively pure THC and crude marijuana extract calibrated to the same dosage of THC have similar effects on

B. THC (N = 7) EXT (N = 4) COMB (N = 11)		
Long-term high dosage	*Initial withdrawal*	*Long-term high dosage vs initial withdrawal (p)*
50.9	27.6	0.01
64.1	32.9	NS
55.7	29.5	0.0005
110.8	141.8	0.005
127.2	152.0	NS
116.8	145.5	0.004
27.2	37.0	0.0008
31.4	41.7	NS
28.7	38.7	0.0002
292.1	641.8	0.002
485.3	802.2	NS
362.4	700.1	0.00009
18.1	30.5	0.0014
25.8	35.6	NS
20.9	32.4	0.0001
2.4	2.7	0.03
2.5	2.7	NS
2.4	2.7	0.003

the sleep EEG. It is highly probably that these effects are produced by the THC and not by some congener or other substance present in both the THC and the extract preparations, but in the absence of pure THC, this possibility cannot be ruled out. If effects on sleep patterns are related to behavior, one would expect THC and extract to produce the same behavioral effects and, in fact, this appears to be the case.

In our previous report,[9] we compared our findings with THC to earlier studies of its effects on sleep. Since the effects of marijuana extract are the same, this discussion need not be repeated here, but we must take note of the recent study by Adams and Barratt.[2] They administered 1.2 mg/kg of THC in a single oral dose each day to squirrel monkeys over 60-day periods and recorded EEG sleep patterns prior to, during, and after the drug. Their results were quite different from ours. They found that THC decreased EEG stages 3 and 4 with no significant effects on REM sleep duration; regrettably, eye movement activity was not reported. If these discrepant results are not due to the differences in dosage and schedule, they point to a difference in sleep response to THC within the primate order.

We previously noted[9] that the findings of Moreton and Davis[20] suggest a species difference, in this case, between man and rats, who found clear REM suppression with THC, but no REM rebound. Such species differences could prove of heuristic interest.

Finally, we add two citations omitted from our previous survey of the literature. Kales, Hamley, and Rickles[14] reported that smoking of marijuana suppressed REM sleep duration initially; continued smoking was associated with return to baseline and a rebound increase above baseline followed withdrawal. It is unfortunate that these findings are available only in abstract form, since this is one of the few studies reporting measurable brain effects of marijuana under dosages in social use. Pranikoff and associates[22] found low values for stages 3 and 4 and normal values for REM sleep in a group of long-term marijuana users.

We have proposed that sedative-hypnotic drugs produce two main effects on sleep: suppression of eye movement activity (i.e., reduced EM density) and, with repeated administration, of stage 4 sleep, and that the time-courses of these effects differ.[11] The available literature supports this view for two major subclasses of sedative-hypnotics: the barbiturates and the benzodiazepines.[8] Under our conditions of administration and dosage, THC and marijuana produce as marked a suppression of EM as do barbiturates and benzodiazepines when the latter are given before sleep in hypnotic doses (e.g., 100 mg secobarbital, or 30 mg flurazepam). Withdrawal of THC and marijuana produces moderate elevations of REM duration above baseline ("rebounds") and much more marked increases in eye movement activity. Sedative-hypnotic withdrawal is often claimed to cause REM sleep rebounds,[15, 21] but clear-cut experimental sup-

Table IV. *Measures of NREM sleep for THC and marijuana extract, separately and combined*

	A. THC (N = 4) EXT (N = 2) COMB (N = 6)					
	Baseline (b)	*Low dosage (l)*	*Initial high dosage (i)*	*Long-term high dosage (h)*	*Initial withdrawal (w)*	*Long-ter withdraw*
Percent NREM						
THC	67.6	74.6[b]	—	71.2[b]	60.5[l,h]	—
EXT	70.6	73.1	74.5	71.7	54.9	67.5
COMB	68.6	73.9[b]	—	71.3[b]	58.6[b,l,h]	—
Total stage 2 (20-sec epochs)						
THC	595.7	646.0	—	576.6	509.7	—
EXT	642.5	676.2	726.5	603.5	380.8[l]	537.7
COMB	611.3	656.1[b]	—	585.6[l]	466.7[b,l,h]	—
Percent stage 2						
THC	68.3	69.5	—	67.2	70.0	—
EXT	71.4	72.9	77.7	68.2[i]	60.1[l]	63.8[l]
COMB	69.4	70.7	—	67.5	66.7	—
Total stage 3 (20-sec epochs)						
THC	153.6	139.6	—	116.3[l]	101.1[b,l]	—
EXT	133.1	110.4	81.6	129.8	148.0[h]	136.2
COMB	146.8	129.8	—	120.8	116.7	—
Percent stage 3						
THC	17.8	15.3	—	13.7	15.1	—
EXT	14.8	11.7	8.4	15.0	23.6[b]	16.2[v]
COMB	16.8	14.1	—	14.1	17.9	—
Total stage 4 (20-sec epochs						
THC	122.5	142.8	—	167.8	106.9	—
EXT	130.9	153.5	138.2	150.0	101.8	180.4
COMB	125.3	146.4	—	161.9	105.2[l,h]	—
Percent stage 4						
THC	13.9	15.2	—	19.1[l]	14.9	—
EXT	13.8	15.4[b]	14.0	16.8	16.4	19.9
COMB	13.8	15.2	—	18.4[l]	15.4	—
Total delta sleep						
THC	276.1	282.4	—	284.2	208.0[l,h]	—
EXT	264.0	263.8	219.8	279.8	249.8	316.5
COMB	272.1	276.2	—	282.7	221.9[h]	—
Percent delta sleep						
THC	31.7	30.5	—	32.8	30.0	—
EXT	28.6	27.1	22.3	31.8[i]	39.9[l]	36.2[b]
COMB	30.6	29.3	—	32.5	33.3	—

p values are based on paired, 2-tailed t tests. Group means are based on means for 3 nights for each S for each condition.

b,*b* differs from baseline $p < 0.05$, $p < 0.01$, resp.

l,*l* differs from low dosage $p < 0.05$, $p < 0.01$, resp.

i,*i* differs from initial high dosage $p < 0.05$, $p < 0.01$, resp.

h,*h* differs from long-term high dosage $p < 0.05$, $p < 0.01$, resp.

w,*w* differs from initial withdrawal $p < 0.05$, $p < 0.01$, resp.

port for this view is lacking.[8] Nevertheless, it should be recalled that in our experiments reported here, THC and marijuana were given every 4 hr in substantial doses for 20 days. These conditions of administration maximize the probability of developing tolerance and, consequently, withdrawal effects. It remains possible that if barbiturates and benzodiaz-

B. THC (N = 7) EXT (N = 4) COMB (N = 1)		
Long-term high dosage	*Initial withdrawal*	*Long-term high dosage vs initial withdrawal (p)*
72.8	63.0	0.0008
68.6	58.3	NS
71.3	61.3	0.0002
567.7	474.7	0.02
582.3	430.7	NS
573.0	458.7	0.002
64.2	64.7	NS
69.4	66.5	NS
66.1	65.4	NS
110.6	98.9	0.04
130.6	133.0	NS
117.9	111.3	NS
12.6	14.1	0.01
15.8	21.4	0.07
13.8	16.8	0.01
208.6	154.0	0.007
124.1	78.2	0.02
177.9	126.4	0.0002
23.2	21.1	NS
14.7	12.1	NS
20.1	17.9	NS
319.2	252.9	0.002
254.7	211.2	NS
295.8	237.7	0.0001
35.8	35.3	NS
30.6	33.5	NS
33.9	34.6	NS

epines were given around the clock in appropriate dosage, they too would give rise to withdrawal REM rebound as marked as that with THC.

The question of whether the effects of THC on eye movement during sleep are qualitatively as well as quantitatively similar to those of sedative-hypnotics is of basic pharmacologic interest. If these effects are qualitatively and quantitatively the same, they could not by themselves be responsible for the sedative-hypnotic withdrawal syndrome of insomnia, convulsions, and delirium, since this syndrome has not been described after cannabis withdrawal. It is possible that the effects on EM activity of the two drug classes are mediated by qualitatively different mechanisms. We have pointed out elsewhere[8] that EM suppression by sedative-hypnotics may represent a direct effect on oculomotor systems which simply becomes apparent during sleep rather than an action on mechanisms which control REM sleep.

It is equally plausible that the effects of sedative-hypnotics and THC on REM sleep are produced by the same mechanisms. In this case, if sleep patterns are correlated with brain mechanisms underlying the delirium caused by withdrawal of sedative-hypnotics, these relations must be to NREM processes, either alone or in interaction with REM mechanisms. THC clearly differs from sedative-hypnotics in that it does not suppress stage 4 sleep with repeated administration; instead, stage 4 tends to increase with THC. Even during the REM rebound of THC withdrawal, where stage 4 falls significantly below high-dosage levels, it is not reduced below baseline. This difference may be crucial to the difference in ability to produce withdrawal delirium. This speculation is weakened, however, by the fact that benzodiazepines suppress stage 4 sleep to an even greater extent than barbiturates (and EM activity to a similar degree). Nevertheless, benzodiazepines seem less likely than barbiturates to lead to withdrawal delirium. We might also note, in passing, that the enormous differences in lethality between barbiturates and benzodiazepines are not reflected in differences in effects on sleep.

Marijuana and THC differ from sedative-hypnotics in that they do not stimulate precentral fast EEG activity or do so to a much smaller extent. This difference may be observed during both sleep and waking and thus is not specific to sleep. We have speculated[9] that the capacity to stimulate fast EEG activity may be correlated with suppression of stage 4 sleep, a conjecture that remains to be tested.

We have hypothesized that the different

Table V. *Effects of high dosage and withdrawal compared with baseline on sleep cycles for THC and marijuana extract combined*

		Sleep cycle ($NREMP_1 + REMP_1$, $NREMP_2 + REMP_2$, ..., $NREMP_4 + REMP_4$)			
Sleep measure	*Condition*	*1 (N)**	*2 (N)*	*3 (N)*	*4 (N)*
Total NREM (min)	Baseline	73.0(6)	74.2(6)	67.2^{2}(6)	$54.8^{2,3}$(6)
	High dosage	55.7	78.7^{1}	71.1^{1}	63.7†(8)
	Withdrawal	$29.8^{b,h}$	$67.0^{1,h}$	66.3^{1}	53.9†(9)
Total stage 4 (20-sec epochs)	Baseline	83.9(6)	27.9^{h}(6)	$7.4^{1,2}$(6)	$5.4^{1,2}$(6)
	High dosage	67.6	60.2	$21.8^{1,2}$	23.0†(8)
	Withdrawal	$24.6^{b,h}$	51.6^{1}	29.6	16.0†(9)
REM time (min)	Baseline	20.4(6)	35.5^{1}(6)	37.3^{1}(6)	43.0†(5)
	High dosage	19.2	25.4	30.9†(10)	34.4†(7)
	Withdrawal	30.5	38.5^{h}	35.6†(10)	37.8†(7)
EM density	Baseline	0.122(6)	0.194^{1}(6)	0.227^{1}(6)	0.266†(5)
	High dosage	0.163	0.201	0.215†(10)	0.234†(7)
	Withdrawal	$0.279^{b,h}$	$0.291^{b,h}$	$0.334†^{h}$(10)	$0.347†^{h}$(7)

Group means are based on means for 3 nights for each S for each condition.

1,1 differs from cycle 1 value for same condition, $p \leq 0.05$, $p \leq 0.01$, resp., paired t tests.

2,2 differs from cycle 2 value for same condition, $p \leq 0.05$, $p \leq 0.01$, resp., paired t tests.

3 differs from cycle 3 value for same condition, $p \leq 0.05$, $p \leq 0.01$, resp., paired t tests.

b,*b* differs from baseline mean for same cycle, $p \leq 0.05$, $p \leq 0.01$, resp.; based on unpaired, 2-tailed, pooled-variance t tests.

h,*h* differs from high-dosage mean for same cycle, $p \leq 0.05$, 0.002 resp., paired t tests.

*N = 11 except where shown otherwise in ( ).

†Paired comparisons not made for values with differing Ns.

classes of psychoactive drugs might exert different patterns of effects on EEG sleep patterns ("specificity hypothesis"[8, 11]). This notion was intended to apply to drug classes whose members, while sometimes differing chemically, have common behavioral effects that may be presumed the consequence of similar brain mechanisms, i.e., the classes of sedative-hypnotics, antidepressants, analeptics, antischizophrenic agents, lithium, and opiates. Recently, Gaillard and Aubert[12] conjectured that characteristically different effects on sleep should be produced by drugs having the same behavioral effects but that belong to different chemical classes, e.g., barbiturates and benzodiapines. This difference is inconsistent with the literature cited above and elsewhere.[8] Moreover, it is not supported by the observations of Gaillard and Aubert. Their work shows, instead, that oxazepam and phenobarbital induced identical patterns of effects on stage 4 and EM density. They concluded that these drugs differed qualitatively because the significance levels of within-drug comparisons were different, an interpretation that simply does not follow.

Comparing the effects of THC on human sleep with those reported for other drug classes in the light of the "specificity hypothesis," we find that THC resembles lithium most. Lithium, given in therapeutic dosages to patients with affective disorders, also increases stage 4 sleep and decreases EM density.[3, 17–19] The former effect appears to be more powerful, and the latter effect somewhat weaker, than the corresponding effects produced by THC under our experimental conditions. However, lithium differs clearly from THC and marijuana extract in that it does not induce either REM rebound or a sharp fall in stage 4 sleep upon withdrawal. These differences may reflect a qualitative difference in the mechanisms that induce the sleep effects (presumably, alterations in neurotransmitter states in the case of THC), or they may simply reflect differences in rates of clearance. (The kinetics of psychoactive drug effects on sleep, i.e., rates of induction, of development of tolerance and of clearance,

have not yet received systematic study.) If the sleep effects of THC differ qualitatively from those of lithium, they would be unique among the drugs studied thus far.

If THC and lithium effects on sleep are produced by similar brain mechanisms, this finding would provide a rationale for the experimental administration of THC to patients with manic-depressive illnesses. Ablon and Goodwin[1] have shown that THC in doses of 5 to 40 mg daily for up to 7 days produces marked dysphoric reactions in patients with unipolar depressive illness but little effect in depressed bipolar patients. These differences raise the possibility that THC in larger doses could provide a diagnostic test to distinguish between bipolar and unipolar depression, a distinction of increasing clinical importance. In addition, a controlled experiment of the efficacy of THC in the treatment of bipolar affective illness may merit consideration.

In summary, our data show that under the conditions of our studies, THC and marijuana extract produce similar and powerful effects on brain activity during sleep. It is frustrating that these effects cannot immediately be related to behavior and that their neurophysiological significance is also obscure. However, the effects on sleep physiology are substantial and should prove a valuable tool in the study of sleep pharmacology. The more general question of whether the marked effects produced on sleep by psychotropic agents are related to mechanisms of therapeutic action or are the "common end results of diverse neurochemical changes"[9] remains to be evaluated.

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